REMARKS

Claims 1-7 and 10-18 are pending in the present application. As will be discussed below, Claims 1 and 11 have been amended and Claims 16-18 have been added. No new matter has been added. Accordingly, entry of the present Amendment is requested.

Applicants acknowledge that the Restriction Requirement has been withdrawn.

With respect to the Examiner's comments regarding domestic priority under 35 U.S.C. § 120, in accordance with MPEP §1893.03(d), Applicants have not amended the first page of the specification to refer to the prior international application. The present application is a national stage application under 35 U.S.C. § 371 and in accordance with Chapter II of the Patent Cooperation Treaty, as indicated in the request for the present application on December 12, 2000. Accordingly, the date of filing of the present application is the date of filing of the international application.

With regard to the objections noted on page 4 of the Office Action, the specification has been amended in accordance with the Examiner's helpful suggestion. In addition, the typographical error in Claim 11 has been corrected and an Abstract has been provided. Accordingly, withdrawal of the objections is requested.

Claims 1-7 and 10-15 have been rejected under 35 U.S.C. § 112, first paragraph. It is asserted that the specification, while being enabling for covalent binding of rT3 to human insulin residues B29 Lys and B1 Phe, assertedly does not reasonably provide enablement for covalent bonding of rT3 to any insulin molecule at any residue, or to any lysine at any residue of any insulin, or to any amino acid of B1 residue of any insulin.

In response, the claims have been amended to specify that the insulin molecule is covalently bound "through an amide bond formed between an amine group on the insulin molecular and a carboxylic group." This amendment is supported by, for example, page 3, lines 7 to 8. The claims have also been amended to specify that the amine group is an e-amino group of a lysine residue, or is the N-terminal amine group of a polypeptide chain of an insulin. This is supported by, for example, page 2, lines 34 to 35 (lysine residues) and the example where the N-terminal Phe residue of the B chain is reacted with the thyronine molecule.

In view of the foregoing, Applicants respectfully submit that the claims are now more clearly enabled by the specification. A peptide chemist would be enabled to synthesise a conjugate of amine groups of any lysine moiety in an insulin molecule, or either of the N-terminal amine groups of insulin with a carboxyl group of rT3, using the methodology exemplified in the present specification. The specification explains how potentially reactive groups on the protein may be protected during the conjugation reaction in which the amide group is formed. The specification also describes in general terms that residues of the insulin molecule may be deleted or substituted. From publicly available information, the skilled person will be able to select suitable insulin molecules with amine groups to which the thyronine group may be linked, and carry out the linking (conjugation) reaction.

The Examiner asserts that a person skilled in the art is aware that some of the residues of insulin may be deleted. However, contrary to the Examiner's assertion a skilled person does know which residues are essential for insulin-insulin receptor activation. Studies have been conducted, in which each residue of insulin is sequentially substituted by another residue and the effect on activity determined. Applicants respectfully submit that from this information, a

skilled person would be able to predict and then test whether any substitution with an amine-group containing residue for conjugation, would have an effect on activity such that the insulin would be inactive.

In view of the foregoing, withdrawal of this rejection is requested.

Claims 1-7 and 10-15 have been rejected under 35 U.S.C. § 102(a) as being unpatentable over U.S. Patent No. 5,750,497 to Havelund *et al.* (WO-A-95/07931) in view of Weeks *et al* and Ikeda *et al.*

Applicants respectfully traverse this rejection for the following reasons.

As recognized by the Examiner, Havelund does not disclose conjugates of insulin with 3, 3', 5'-triiodothyronine (rT3).

Weeks, as the Examiner points out, teach that rT3 is one of the mono deordination products of T4. rT3 is inactive, by contrast with the alternative product of mono deordination of T4, T3. Ikeda teach that metabolization of T4 to T3 and rT3 takes place in the liver. Weeks and Ikeda do not, however, describe any teaching which is relevant to the question of targeting of any molecule, let alone a thyroid hormone, from the circulation to the liver. The Examiner's suggestion that Weeks and Ikeda teach that rT3 is hepatoselective is not correct. Weeks and Ikeda refer to the activity of rT3 and related compounds, T4 and T3, as thyroid hormones. They have no disclosure which is relevant to the activity of insulin. The present invention is relevant to insulin activity and insulin targeting to the liver. In the present invention, the relevant activity of the rT3 component of the conjugate is not as a thyroid hormone, but rather as a binding moiety for circulating binding proteins. There is nothing in Weeks or Ikeda that would suggest that either T3 or rT3 would be a suitable replacement for the T4 moiety in the conjugate in

Havelund. The activity of the T4 moiety in Havelund is not even described. Certainly it is not described as having activity as a thyroid horomone. Thus, the teachings of Weeks and Ikeda regarding the activity, or of rT3 in terms of thyroid hormone activity is totally irrelevant.

Applicants respectfully submit that it is purely hindsight which has led to the rejection, and even with hindsight, the reasoning does not lead to the invention. There is nothing to suggest that rT3 conjugated to another molecule would have the function of directing that other molecular in the blood to the liver, still less comparing this performance with that of T4.

In view of the foregoing, withdrawal of the rejection is requested.

Claims 1-7 and 10-15 have also been rejected under the doctrine of obviousness-type double patenting over Claims 1-3 and 5-12 of U.S Patent No. 5,854,208 in view of Ikeda and Havelund. Applicants respectfully traverse this rejection for the same reasons expressed above and the following additional reasons.

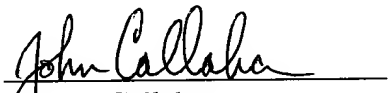
The genus in Jones, of thyroid hormones, and the species of T4, do not teach the specific compound rT3, nor render it obvious. Applicants have shown that there is a surprising advantage in the performance of the rT3 conjugate over the T4 conjugate. In particular, the potency values in the presence of THBP set out in Example 2, show an advantage of the rT3 conjugates over the T4 conjugates. It is also shown that the potency of rT3-insulin compared to insulin is similar which is very desirable, and contrasts with the increased potency of T4-insulin (in the absence of binding proteins). These advantages are in addition to the reduced likelihood of the rT3 component having activity as a thyroid hormone when administered at relatively high levels as part of the conjugate. By contrast, it is possible that the conjugate, or a breakdown product, could have activity on thyroid hormone receptors which would be undesirable.

Accordingly, withdrawal of this rejection is also requested.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



John T. Callahan
Registration No. 32,607

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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Date: July 9, 2003

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims are amended as follows:

1 (Amended). A compound consisting of an insulin molecule covalently bound to 3, 3', 5' triiodothyronine, wherein the insulin molecule is covalently bound through an amide bond formed between an amine group on the insulin molecule and a carboxylic group, and the amine group is an e-amino group of a lysine residue, or is the N-terminal amine group of a polypeptide chain of an insulin.

11 (Amended). A ~~pharamaceutical~~ pharmaceutical composition comprising a compound according to claim 3 and a pharmaceutically acceptable carrier.

Claims 16-18 are added as new claims.

IN THE ABSTRACT

Please add the following Abstract of Disclosure.

A novel analogue of insulin has covalently conjugated thereto, preferably at the B1 residue, 3, 3', 5'-triiodothyroxine. The conjugate is believed to be hepatoselective, whilst it retains insulin receptor binding properties.